

Non-cirrhotic portal hypertension – Diagnosis and management

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Summary

NCPH is a heterogeneous group of liver disorders of vascular origin, leading to PHT with near normal HVPG. NCPF/IPH is a disorder of young adults or middle aged women, whereas EHPVO is a disorder of childhood. Early age acute or recurrent infections in an individual with thrombotic predisposition constitute the likely pathogenesis. Both disorders present with clinically significant PHT with preserved liver functions. Diagnosis is easy and can often be made clinically with support from imaging modalities. Management centers on control and prophylaxis of variceal bleeding. In EHPVO, there are additional concerns of growth faltering, portal biliopathy, MHE and parenchymal dysfunction. Surgical shunts are indicated in patients with failure of endotherapy, bleeding from sites not amenable to endotherapy, symptomatic hypersplenism or symptomatic biliopathy. Persistent growth failure, symptomatic and recurrent hepatic encephalopathy, impaired quality of life or massive splenomegaly that interferes with daily activities are other surgical indications. Rex-shunt or MLPVB is the recommended shunt for EHPVO, but needs proper pre-operative radiological assessment and surgical expertise. Both disorders have otherwise a fairly good prognosis, but need regular and careful surveillance. Hepatic schistosomiasis, CHF and NRH have similar presentation and comparable prognosis.

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Introduction

Portal hypertension (PHT) is a clinical syndrome defined by a portal venous pressure gradient between the portal vein (PV) and inferior vena cava exceeding 5 mmHg [1]. Cirrhotic PHT is associated with an elevated hepatic venous pressure gradient (HVPG) predominantly due to raised sinusoidal resistance, while in the non-cirrhotic PHT (NCPH), HVPG is normal or only mildly elevated and is significantly lower than PV pressure. The diseases leading to NCPH are primarily vascular in nature and classified anatomically on the basis of site of resistance to blood flow, as prehepatic, hepatic, and post-hepatic – hepatic causes are further subdivided into pre-sinusoidal, sinusoidal and post-sinusoidal (Table 1) [2,3]. Most of the times, PHT is a late manifestation of the primary disease. However, non-cirrhotic portal fibrosis (NCPF) and extra-hepatic PV obstruction (EHPVO) are two disorders, which present only with features of PHT without any evidence of significant parenchymal dysfunction [2–5]. In this review, an updated account of these two clinical entities along with some of the other causes will be presented.

Non-cirrhotic portal fibrosis (NCPF)

Non-cirrhotic Portal Fibrosis (NCPF) variously called as Idiopathic PHT (IPH), hepatoportal sclerosis and obliterative venopathy, is a disorder of unknown etiology, clinically characterized by features of PHT; moderate to massive splenomegaly, with or without hypersplenism, preserved liver functions, and patent hepatic and portal veins [2,3] (Table 2).

The disease has been reported from all parts of the world, more so from the developing countries [6–16]. According to the consensus statement of the Asia Pacific Association for the Study of the Liver (APASL) on NCPF, the disease accounts for approximately 10–30% of all cases of variceal bleed in several parts of the world including India [17]. It is more common in young males in third to fourth decades belonging to low socioeconomic groups [2,9–13]. A disease mimicking NCPF, known as IPH in Japan and idiopathic non-cirrhotic PHT in the West, has female preponderance and presents around the fifth decade [7,14–16] (Table 3). Such demographic variations could be due to differences in the living conditions, ethnicity, average life span, reporting bias as well as on the diagnostic criteria utilized. There are speculations of decreasing incidence of the disease, which is possibly related to improved standards

Keywords: Portal hypertension; Non cirrhotic portal fibrosis; Extrahepatic portal venous obstruction; Portal biliopathy; Shunt surgery.

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Abbreviations: APASL, Asia Pacific Association for the Study of the Liver; CHF, congenital hepatic fibrosis; CSRS, PSRS, DSRS, central, proximal, and distal spleno-renal shunt; EHPVO, extrahepatic portal venous obstruction; ERCP, endoscopic retrograde cholangiopancreatography; EST, endoscopic sclerotherapy; EVL, endoscopic variceal ligation; HIV, human immunodeficiency virus; HPS, hepatopulmonary syndrome; HVPG, hepatic venous pressure gradient; INCPH, idiopathic non-cirrhotic portal hypertension; IPH, idiopathic portal hypertension; LTx, liver transplantation; MHE, minimal hepatic encephalopathy; MLPVB, mesenteric left portal vein bypass or Rex shunt; MRCP, magnetic resonance cholangiopancreatography; NCPF, non-cirrhotic portal fibrosis; NCPH, non-cirrhotic portal hypertension; NRH, nodular regenerative hyperplasia; PHT, portal hypertension; PV, portal vein; PVT, portal vein thrombosis; QoL, quality of life; UVC, umbilical vein catheterization.

Review

Table 1. Causes of Non-cirrhotic portal hypertension (NCPH).

| | | |
|--|---|--|
| Pre-hepatic | | |
| FHVP normal, RAP normal, WHVP normal, HVPG normal, PVP high, ISP high | | |
| Extrahepatic portal vein obstruction (EHPVO) | | |
| Portal vein thrombosis | | |
| Splenic vein thrombosis | | |
| Splanchnic arteriovenous fistula | | |
| Massive splenomegaly | | |
| Infiltrative diseases-Lymphoma, myeloproliferative disorders | | |
| Storage diseases-Gaucher's disease | | |
| Hepatic | | |
| FHVP normal, RAP normal, WHVP high, HVPG normal or high, PVP high, ISP high* | | |
| Pre-sinusoidal | Sinusoidal | Post-sinusoidal |
| Developmental abnormalities | Sinusoidal fibrosis | Venoocclusive disease |
| Adult polycystic disease | Alcoholic hepatitis | Hepatic irradiation |
| Hereditary hemorrhagic disease | Drugs (methotrexate, amiodarone) | Toxins-Pyrrolizidine alkaloids |
| Arteriovenous fistulas | Toxins (vinyl chloride, copper) | Drugs-Gemtuzumab, ozogamicin, actinomycin D, dacarbazine, cytosine arabinoside, mithramycin, 6-thioguanine, azathioprine, busulfan plus cyclophosphamide |
| Congenital hepatic fibrosis | Metabolic (NASH, Gaucher's disease) | |
| Biliary diseases | Inflammatory (viral hepatitis, Q fever, healed cytomegalovirus, secondary syphilis) | |
| Primary biliary cirrhosis | | |
| Sclerosing cholangitis | | |
| Autoimmune cholangiopathy | Sinusoidal collapse | Phlebosclerosis of hepatic veins |
| Toxic-Vinyl chloride | Acute necro-inflammatory diseases | Alcoholic liver disease |
| Neoplastic occlusion of portal vein | Sinusoidal defenestration | Chronic radiation injury |
| Lymphoma | Alcoholic liver disease (early phase) | Hypervitaminosis A |
| Epithelioid hemangioendothelioma | Sinusoidal infiltration | E-ferol injury |
| Epithelial malignancies | Mastocytosis | Primary vascular malignancies |
| Chronic lymphocytic leukemia | Agnogenic myeloid metaplasia | Epithelioid hemangioendothelioma |
| Granulomatous lesions | Gaucher's disease | Angiosarcoma |
| Schistosomiasis | Amyloidosis | Granulomatous phlebitis |
| Mineral oil granuloma | Sinusoidal compression | Sarcoidosis |
| Sarcoidosis | By enlarged Kupffer cells (Gaucher's disease, visceral Leishmaniasis) | Mycobacterium species |
| Hepatoportal sclerosis | By enlarged fat-laden hepatocytes (Alcoholic hepatitis, AFLP) | Lipogranulomas |
| Peliosis hepatitis | | Mineral oil granuloma |
| Partial nodular transformation | | Hepatic vein outflow tract obstruction (HVOTO, Budd-Chiari syndrome)-Idiopathic, prothrombotic states |
| Noncirrhotic portal fibrosis (NCPF)/ | | |
| Idiopathic portal hypertension (IPH) | | |
| Post-hepatic | | |
| FHVP high, RAP normal or high, WHVP high, HVPG normal or high, PVP high, ISP high** | | |
| Inferior vena cava obstruction-web, thrombosis, tumour, enlarged caudate lobe | | |
| Constrictive pericarditis | | |
| Tricuspid regurgitation | | |
| Severe right-sided heart failure | | |
| Restrictive cardiomyopathy | | |

*HVPG not feasible in HVOTO with occlusion of all 3 hepatic veins, or supra- and intrahepatic inferior vena cava obstruction.

**Inferior vena cava pressure should also be taken both above and below the opening of hepatic veins.

AFLP, acute fatty liver of pregnancy; FHVP, free hepatic venous pressure; HVPG, hepatic venous pressure gradient (difference between FHVP and WHVP); ISP, intrasplenic pressure; NASH, non-alcoholic steatohepatitis; PVP, portal vein pressure; RAP, right atrial pressure; WHVP, wedged hepatic venous pressure.

of hygiene and perinatal care leading to reduction in incidences of umbilical sepsis and diarrheal episodes in early childhood [17].

Etiopathogenesis

The precise etiopathogenesis of NCPF/IPH is an area of ongoing research. Infections and prothrombotic states are commonly

incriminated in the eastern and western patients, respectively [2].

Etiological factors

Rarity of the disease in the west, a declining trend with improved standards of living and hygienic conditions support the role of infections, of imprecise nature, at an early age in the disease path-

Table 2. Diagnostic criteria for non-cirrhotic portal fibrosis/idiopathic portal hypertension.

| Japanese criteria for IPH [7] | APASL criteria for NCPF/IPH [17] | Schouten JNL <i>et al.</i> , Hepatology 2012 for INCPH [3] [§] |
|---|---|--|
| <ul style="list-style-type: none"> Clinical disorder of unknown etiology with Splenomegaly, anemia and portal hypertension with Absence of cirrhosis, blood disease, parasites in the hepatobiliary system, and occlusion of the hepatic and portal veins | <ul style="list-style-type: none"> Presence of moderate to massive splenomegaly Evidence of portal hypertension, varices, and/or collaterals Patent spleno-portal axis and hepatic veins on ultrasound Doppler Test results indicating normal or near-normal liver functions Normal or near-normal HVPG Liver histology-no evidence of cirrhosis or parenchymal injury | <ul style="list-style-type: none"> Clinical signs of portal hypertension (any one of the following): <ul style="list-style-type: none"> Splenomegaly/hypersplenism[#] Esophageal varices Ascites (non-malignant) Increased HVPG Portovenous collaterals Exclusion of cirrhosis on liver biopsy Exclusion of known causes of chronic liver disease causing cirrhosis or non-cirrhotic portal hypertension^{##} <ul style="list-style-type: none"> Chronic viral hepatitis B and/or C Non-alcoholic steatohepatitis Alcoholic steatohepatitis Autoimmune hepatitis Hereditary hemochromatosis Wilson's disease Primary biliary cirrhosis Exclusion of common conditions causing non-cirrhotic portal hypertension <ul style="list-style-type: none"> Congenital hepatic fibrosis Sarcoidosis Schistosomiasis Patent portal and hepatic veins (on Doppler ultrasound or computed tomography scanning) |
| Additional points* | Other features: | [§] All five criteria must be fulfilled to diagnose idiopathic non-cirrhotic portal hypertension (INCPH) [#] Splenomegaly must be accompanied by additional signs of portal hypertension to fulfill this criterion ^{##} Chronic liver disease must be excluded, because severe fibrosis might be understaged on liver biopsy |
| <ol style="list-style-type: none"> Normal to near-normal liver function tests Varices demonstrable by endoscopy or radiography Decrease of one or more of the formed blood elements Liver scan not typical of cirrhosis Patent hepatic veins with a normal to slightly elevated WHVP Grossly non-cirrhotic liver surface Hepatic histology not indicative of cirrhosis Patent extrahepatic portal vein with frequent collateral vessels Elevated portal pressure <p>*Not all these investigations are required for diagnosis</p> | <ol style="list-style-type: none"> Absence of signs of chronic liver disease No decompensation after variceal bleed except occasional transient ascites Absence of serum markers of hepatitis B or C virus infection No known etiology of liver disease Imaging with ultrasound or other imaging techniques showing dilated and thickened portal vein with peripheral pruning and periportal hyperechoic areas | |

ogenesis [2,18]. Endotoxin mediated injury with or without induced autoimmunity is the proposed hypothesis [19]. Role of *prothrombotic disorders* in the pathogenesis is supported by autopsy studies showing high prevalence of PV thrombosis (PVT) and studies from the west indicating association with prothrombotic states [14,15]. However, PVT being not a universal event, absence of acute manifestations of PVT and presence of increased blood flow in the splenic vein are pointers, which negate this hypothesis. Prolonged exposure to several *medications and toxins* especially arsenic has also been incriminated as a cause [2,3,20,21]. *Immunological* basis is propagated due to female preponderance, association with various immunological

and autoimmune disorders, and presence in serum of various autoantibodies [22]. Lastly, familial clustering, association with human leukocyte antigen (HLA)-DR3 and with some genetic syndromes suggest a *genetic* basis [3,23].

Animal studies

Various animal models suggesting an infective and immune basis are shown in Fig. 1 [18,24,25]. NCPF animals develop splenomegaly, high portal pressures, low mean arterial pressures with normal liver functions and histology, demonstrating the role of vascular compartment in causing PHT. Also, in the chronic arsenic

Review

Table 3. Epidemiology, clinical features and survival of NCPF/IPH-related disorders by various workers over last 3 decades.

| Study (yr) [Ref.] | Aoki (1998) [7] | Vakili (1992) [9] | Sarin, Pandey (1998, 2006) [10,12] | Dhiman (2002) [11] | Madhu (2009) [13] | Hillaire, Cazals- Hatem (2002, 2011) [14,15] | Schouten (2012) [16] |
|-----------------------------|--------------------|---|--|-----------------------|----------------------|--|----------------------------|
| Country | Japan | Iran | India | India | India | France | Netherlands and Belgium |
| No. of subjects | 671 | 32 | 207, 336 | 151 | 30 | 28, 46 | 62 |
| Proportion of total PHT (%) | ~33% | 21% | 9.7% | 15% | 13.2% | - | - |
| Male:Female | 1:3 | 1.5:1 | 1.3:1, 1:1 | 1:1.65 | 1.7:1 | 2.5: 1, 2:1* | 1.06:1 |
| Mean age at diagnosis (yr) | 49.9 | 3 rd -4 th decade | 30.7, 31.6 | 30.5 | 32 | 41.8, 38.5* | 46 |
| Duration of symptoms | - | 1 mo-18 yr | - | 15 d-336 mo | - | - | - |
| Clinical features | | | | | | | |
| Mass LUQ | - | - | 12% | 69% | - | - | - |
| Splenomegaly | - | - | 74% | 97% | 60% (with anemia) | 36%, 26%* | 28% |
| Anemia | - | - | 90% | - | - | - | - |
| Variceal bleed | - | 84% | 72% | 65% | 43% | 32%, 32%* | 55% |
| Palpable liver | - | 33% | 84.5% | 54% | - | - | - |
| Decompensation | - | - | - | 8.6% | - | - | 19% |
| Ascites | - | 25% | 25% | 9.9% | 10% | - | 34% |
| Edema | - | - | 10%, 18% | 4% | - | - | - |
| Laboratory features | | | | | | | |
| Hypersplenism | - | - | 27% | 45.6% | 87% | 37%* | - |
| Abnormal LFT | - | 25% | 32%, 2% | 18% | 73% | 28.6%, 14%* | - |
| High bilirubin | - | 31% | - | 8.8% | - | -, 30%* | - |
| Deranged INR | - | 81% | 78% | 3.9% | 27% | -, 14%* | - |
| Hypoalbuminemia | - | - | - | 16.8% | - | -, - | - |
| Hemodynamics | | | | | | | |
| HVPG >5 mmHg | - | - | - | - | 71% | 61.5%, 65% | - |
| HVPG (median) | - | - | 7 mmHg | - | 12.5 mmHg | 6, 7 mmHg* | - |
| Histopathology | | | | | | | |
| Phleboscrosis | - | - | - | 100% | - | 39%, 96%* | 98% |
| Dilated portal venules | - | - | - | 42% | 50% | -, 38%* | 69% |
| PP fibrosis | - | - | - | 30% | 63% | 32%, 30%* | - |
| PS fibrosis | - | - | - | - | 17% | 32%, 57%* | 94% |
| NRH | - | - | - | - | - | 18%, 70%* | 47% |
| Dilated sinusoids | - | - | - | - | - | -, - | 98% |
| Endoscopic features | | | | | | | |
| Esophageal varices | - | - | 92%, 97% | - | - | 43%, 33%* | - |
| Gastric varices | - | - | 22.3%, 31% | - | - | - | - |
| Gastropathy | - | - | 1.6%, | - | - | - | - |
| Colopathy | - | - | 40% | - | - | - | - |

*Reference [15] included both patients with obliterative portal venopathy and extra-hepatic portal venous obstruction.

INR, international normalized ratio; LFT, liver functions tests; LUQ, left upper quadrant; NRH, nodular regenerative hyperplasia; PP, portal-portal; PS, portoseptal; d, days; mo, months; yr, years.

exposure model, there is increased hydroxyproline and collagen without significant hepatic fibrosis [26].

Pathogenesis

Various theories to explain the pathogenesis of NCPF/IPH have been proposed and are mentioned in Fig. 2 [2,3,27].

Pathology

Liver pathology is characterized by phleboscrosis, fibroelastosis, periportal, and perisinusoidal fibrosis, aberrant vessels in portal tract (portal angiomatosis), preserved lobular architecture, and differential atrophy [6,28,29]. Main PV trunk is dilated with thick sclerosed walls, along with thrombosis in medium and small PV branches – the histological hallmark termed “oblitera-

tive portal venopathy” [6,29]. Nakanuma *et al.* had proposed a staging system based on gross and imaging features: stages I–IV, stage I being absence of peripheral parenchymal atrophy; stage IV showing presence of obstructive thrombosis in intrahepatic large branches or trunk of PV [29]. Spleen is disproportionately large (average weight 723 g) at portal pressures comparable to other conditions of PHT [11].

Extra-hepatic portal venous obstruction (EHPVO)

Extra-hepatic portal venous obstruction (EHPVO) is a childhood disorder characterized by a chronic blockage of PV blood supply leading to PHT and its sequelae in the setting of a well preserved

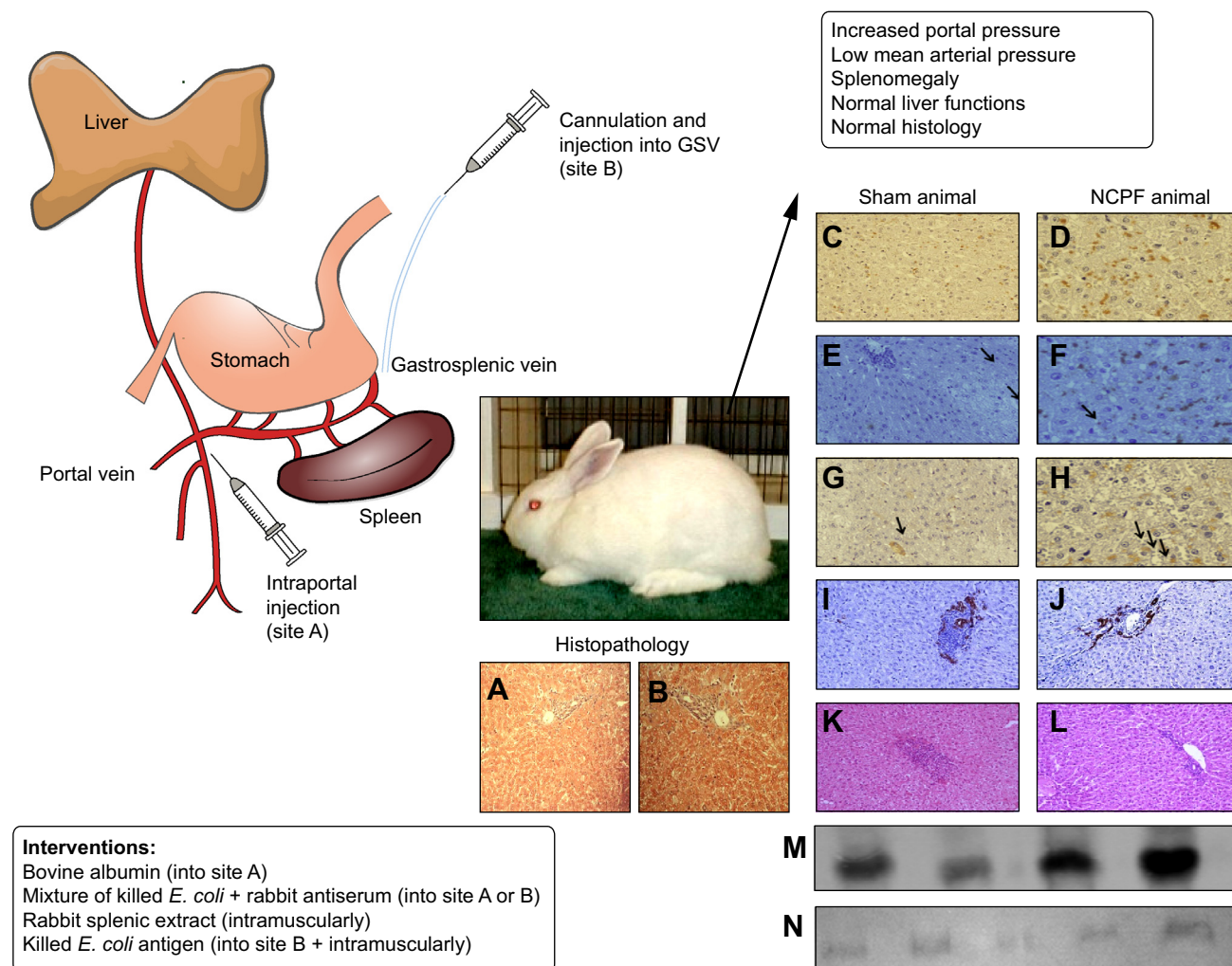


Fig. 1. Animal models of NCPF/IPH. Rabbit models using various interventions either intraportally or via indwelling cannula into gastrosplenic vein or intramuscularly have been developed [18,24,25]. Studies using albumin [24] and splenic extract [25] favor an immunological basis for NCPF/IPH, whereas those using *E. coli* favor an infective basis [18]. We have developed an Endotoxemia Induced PHT (EIPHT) model of NCPF by administering *E. coli* antigen intramuscularly followed by repeated injections of the same via gastrosplenic vein (GSV) [19]. In comparison to sham operated animals, NCPF animals have comparable liver histology on hematoxylin and eosin staining (B vs. A), but there is overexpression of CD34 (J vs. I), α -SMA (L vs. K), cytokeratin-7 (CK-7), endothelial (eNOS) (D vs. C) and inducible (iNOS) nitric oxide synthase (F vs. E), as well as heme oxygenase (HO)-1 and 2 (H vs. G) enzymes on immunohistochemistry. mRNA as well as protein expression of eNOS, iNOS and HO enzymes were increased on RT-PCR and Western blot (Panel M and N represent protein expression of e-NOS and HO, respectively). Vasoconstriction and vasorelaxation responses to phenylephrine and acetylcholine, respectively, were impaired, suggesting endothelial cell dysfunction [19].

liver function [4]. EHPVO is a major cause of PHT (54%) and upper gastrointestinal bleeding in children (68–84%) from the developing world [30,31]. In the West, non-cirrhotic non-tumoral PVT is the second most frequent cause of PHT in adults [5], whereas in children it constitutes a small proportion (11%) [32].

Definition

As per the APASL consensus, EHPVO is defined as “a vascular disorder of liver, characterized by obstruction of the extra-hepatic PV with or without involvement of intra-hepatic PV radicles or splenic or superior mesenteric veins” [33]. Although, Baveno V consensus definition is more comprehensive and has incorporated recent thrombus as well as portal cavernoma into the definition, there are certain points to be emphasized [34]. EHPVO is a distinct disease entity and should neither be considered an event

in the natural history nor an association of primary liver disease. The term “PVT” includes isolated intrahepatic PVT secondary to cirrhosis or invasion by hepatocellular carcinoma. Also, PVT does not imply formation of portal cavernoma and development of PHT, both of which are inherent to long-standing EHPVO. Similarly, isolated occlusion of the splenic vein or superior mesenteric vein is not included in the definition of EHPVO as the etiological spectrum is different. Since the present review relates to NCPH, ‘recent’ or acute thrombosis or PVT is not discussed.

Etiopathogenesis

Etiological factors differ among pediatric and adult populations and despite extensive history and laboratory work-up, up to 70% of cases may remain idiopathic (Table 4).

Review

Unifying hypothesis

Pathogenic determinants

| | | | |
|---|---------------------------------|-----------------|---------------------------|
| Precipitating event (Infection, trauma, thrombotic event) | | | |
| Prothrombotic predisposition (Genetic or acquired) | | | |
| Nature of insult | Mild, recurring | | Severe, progressive |
| Age | Childhood, adolescence | | Neonatal, early childhood |
| Size of vessel involved | Peripheral portal vein branches | | Main portal vein |
| | | NCPF/IPH | EHPVO |

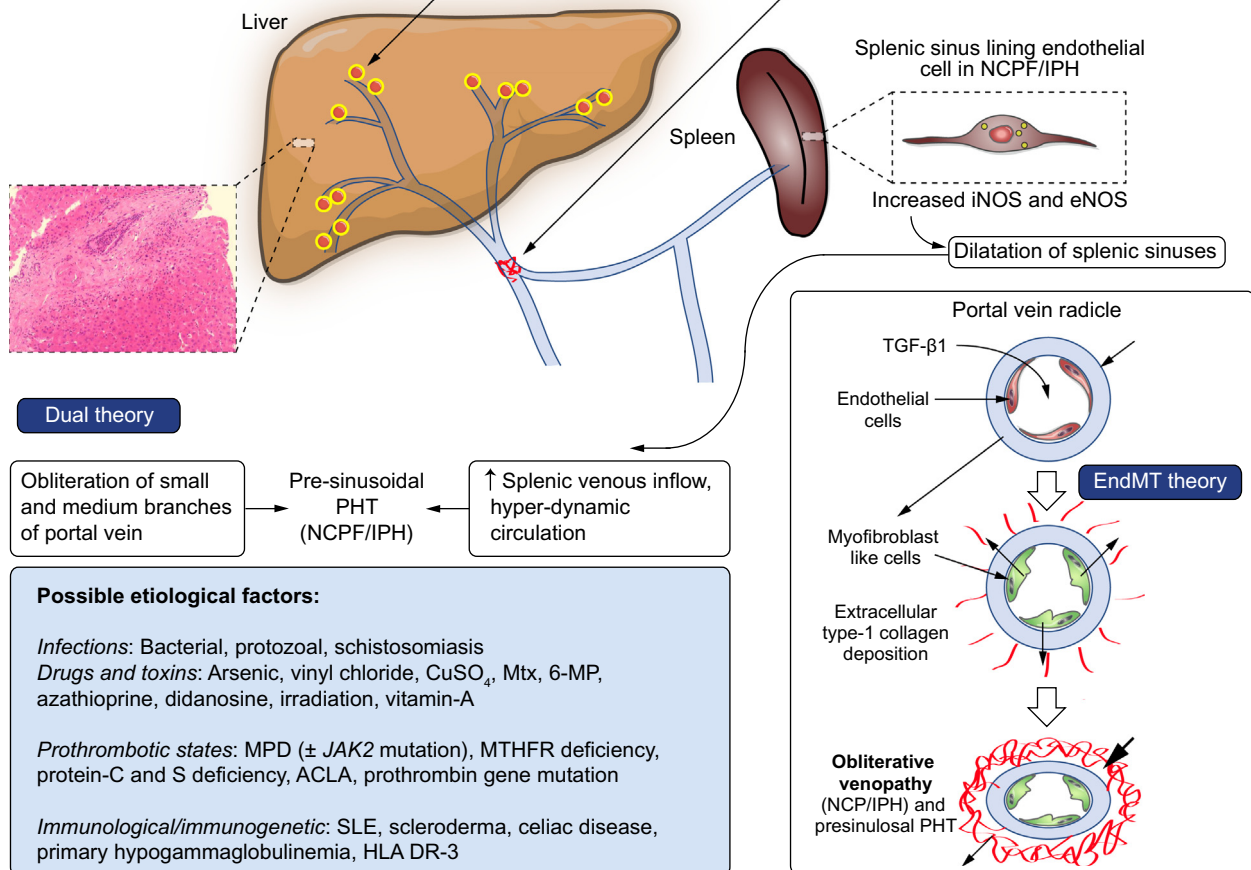


Fig. 2. Pathogenic theories for NCPF/IPH. The *Unifying hypothesis* proposed by Sarin and Kumar gives a common explanation of the pathogenesis of NCPF/IPH and EHPVO [2]. A major thrombotic event occurring at a young age involves main PV and results in EHPVO, whereas repeated microthrombotic events later in life involve small or medium branches of PV leading to NCPF. As per *dual theory* proposed by Schouten *et al.*, both increased splenic blood flow and intrahepatic obstruction (obliterative venopathy) have a role. High levels of inducible (iNOS) as well as endothelial nitric oxide synthase (eNOS) in splenic endothelial cells lead to dilatation of splenic sinuses and increased splenic venous inflow [3]. *Endothelial-mesenchymal transition* (EndMT) theory by Sato and Kitao *et al.* says that vascular endothelial cells of portal venules acquire myofibroblastic features as evidenced by reduced expression of vascular endothelial cell marker CD34, and increased expression of mesenchymal cell markers S100A4, α -SMA, COL1A1, and pSmad2. Transforming growth factor- β 1 (TGF- β 1) acts as a potent inducer of EndMT. Following transformation, these cells synthesize type I collagen, which causes obliterative portal venopathy and presinusoidal PHT [27]. 6-MP, 6-Mercaptopurine; ACLA, anticardiolipin antibody; CuSO_4 , copper sulphate; HLA, human leukocyte antigen; JAK, janus kinase; MPD, myeloproliferative disorders; MTHFR, methylene tetrahydrofolate reductase; Mtx, methotrexate; SLE, systemic lupus erythematosus.

Etiological factors

Like other states of venous thrombosis, the factors leading to EHPVO can be grouped as those within the vessel lumen, within the wall and outside the vessel; and also as prothrombotic states (inherited or acquired) and local factors (trauma, injury, inflammatory conditions). The most common *prothrombotic* states seen in children are methylene tetrahydrofolate reductase (MTHFR)

deficiency (C677T) and prothrombin gene mutations (G20201A), whereas in adults, primary myeloproliferative disorders (MPD) (with or without janus kinase 2, JAK2 mutation V617F) are the commonest. Overall, a single or more prothrombotic states are seen in 28–62% of cases, but none of the studies has screened for all known prothrombotic states [35–59] (Table 4). In a recent meta-analysis, the prevalence of MPD and

JAK2 mutations in PVT was found to be 31.5% and 27.7%, respectively [60]. On the other hand, in a patient with non-malignant non-cirrhotic PVT, the odds ratios of usage of oral contraceptives, or presence of prothrombin gene mutation, factor-V Leiden, or deficiencies of protein-C, protein-S and antithrombin-III are 50, 7, 1.5, 5, 3, and 1, respectively [61]. But, direct extrapolation of these results for EHPVO is unjust. Other conditions leading to EHPVO are *local* abdominal inflammatory and neoplastic conditions and direct or indirect PV injury secondary to accidental or non-accidental trauma or iatrogenic causes subsequent to development of PVT. Lastly, rare congenital and developmental anomalies like PV stenosis, atresia or agenesis can lead to EHPVO, which are usually associated with other malformations, particularly cardiac [4].

Pathogenesis

A unifying hypothesis to explain the pathogenesis of EHPVO has already been mentioned [2] (Fig. 2). Umbilical vein catheterization (UVC) and sepsis are independently present in 9% of EHPVO cases [62]. Although, older studies on neonates with UVC, umbilical sepsis or exchange transfusions have shown conflicting results [63,64], subsequent prospective ultrasound (USG) studies have shown that initial PVT mostly resolves, and progression to EHPVO doesn't occur unless umbilical sepsis is very severe, inadequately treated with antibiotics or UVC is associated with trauma [62,65]. Initial acute PVT event in EHPVO often goes unrecognized and thrombus gradually becomes organized. Multiple hepatopetal collaterals develop around the PV within a span of 6–20 days and develop into a cavernoma in 3 weeks [66]. These collaterals tend to overcome the prehepatic obstruction

and terminate in middle-sized intrahepatic PV branches, thus compensating for a reduction of total hepatic blood flow, but remain insufficient to decompress high pressure in the splanchnic bed. So, hepatofugal vessels do develop at the sites of portosystemic communications and transform into varices, hemorrhoids, and collaterals, some of which may become spontaneous shunts [4].

Animal models

Partial PV ligation is the most widely used animal model to study the hemodynamic changes in EHPVO [67]. However, the limitations are that it is an acute model and prothrombotic states can't be studied in it.

Pathology

There is cavernomatous transformation of the PV – cluster of varying sized vessels replacing PV, arranged haphazardly within connective tissue support at the liver hilum – which may extend for a variable length inside and outside the liver. Architectural pattern of liver is well preserved. Mild periportal fibrosis may be seen [4].

Diagnosis of NCPF and EHPVO

The diagnosis of NCPF and EHPVO is chiefly clinical – presentation with features of PHT without any evidence of liver dysfunction. Patency of hepatic and portal veins is needed for the diagnosis of NCPF/IPH, whereas presence of portal cavernoma on doppler ultrasound (USG) is required for EHPVO. Various

Table 4. Etiological factors in EHPVO and PVT in pediatric and adult studies.

| Etiological factor | Prevalence | | [Ref.] |
|--|-------------------|---------------|------------------------------|
| | Pediatric studies | Adult studies | |
| Primary myeloproliferative disorders: with or without janus kinase 2 (JAK2) mutation (V617F) | 0% | 3-42% | 38, 40, 47-50, 52, 54-58 |
| Factor-V Leiden mutation (rs6025) | 0-30% | 3-14% | 37-41, 47-50, 52-54, 57, 58 |
| Prothrombin gene mutation (G20210A) | 0-15% | 0-21% | 37-41, 47-49, 52-54, 57, 58 |
| MTHFR gene mutation (C677T) | 3-34% | 0-21% | 53 |
| Hyperhomocysteinemia | NE | 11-19% | 54, 57, 58 |
| Protein-C deficiency | 0-45% | 3-41% | 35, 36, 47-49, 52-54, 57, 58 |
| Protein-S deficiency | 0-55% | 2-38% | 35, 36, 47-49, 52-54, 57 |
| Antithrombin III deficiency | 0-50% | 0-41% | 35, 47-49, 52-54, 57, 58 |
| Antiphospholipid syndrome/anticardiolipin antibodies | 3-47% | 1-13% | 36, 38, 40, 49, 54, 57, 58 |
| Paroxysmal nocturnal hemoglobinuria | NE | 0-2% | 49 |
| Local inflammatory conditions | - | | |
| Pancreatitis | 0-5% | 4-19% | 41-46, 49, 51, 52, 57-61 |
| Abdominal sepsis | 6-22% | 5-36% | |
| Liver abscess | 0-3% | 0-4% | |
| Portal vein injury | | | |
| (Trauma, splenectomy, pancreatic surgery, colectomy, etc) | 0-3% | 5-17% | 41-47, 49, 51, 58-61 |
| Umbilical vein catheterization | 0-41% | 0-2% | |
| Umbilical sepsis | 0-45% | <1% | |
| Pregnancy | - | 0-2% | 49, 52, 57, 58 |
| Oral contraceptives | - | 3-19% | 49, 52, 57, 58 |
| Post liver transplant | 8% | 1.5% | 61 |
| Idiopathic | 45-72% | 23-68% | 41-47, 49, 51, 52, 57, 58 |

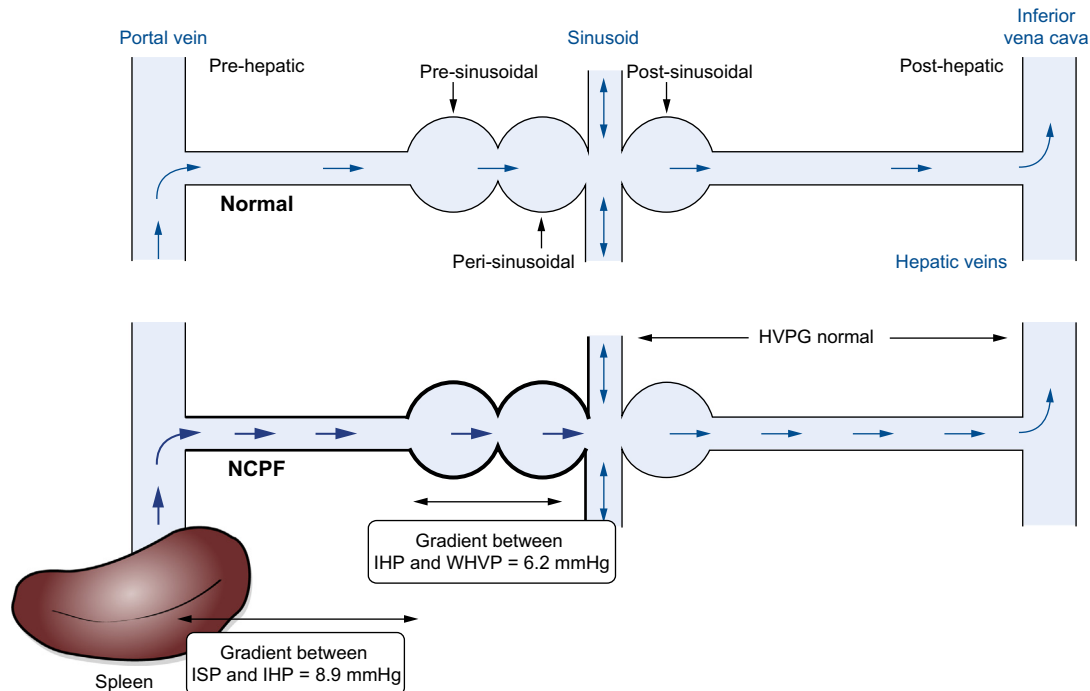


Fig. 3. Hemodynamics in NCPF/IPH. Both intrasplenic (ISP) and intravariceal pressures (IVP) are high in NCPF. There are two independent pressure gradients – one between ISP and intrahepatic pressure (IHP) (8.9 mmHg), and another between IHP and wedge hepatic venous pressure (WHVP) (6.2 mmHg), indicating 2 patho-anatomic sites of resistance in these cases – pre-sinusoidal and peri-sinusoidal. As the vascular resistance is pre- and peri-sinusoidal, HVPG remains nearly normal [79].

diagnostic criteria have been laid down for NCPF/IPH (Table 2). For EHPVO, the diagnosis is as per the APASL definition [33].

Clinical presentation

NCPF/IPH is a disease of young to middle age, whereas EHPVO is primarily a childhood disorder but can present at any age from 6 weeks to adulthood [2,4]. The commonest presentations are well tolerated episodes of variceal bleed, long standing splenomegaly and anemia, and in EHPVO, with accompanied growth retardation (Table 3). In NCPF/IPH, duration of symptoms at presentation varies from 15 days to 18 years [9,11]. Frequency of variceal bleeding episodes increase with age with a median of 1 bleeding episode (range 1–20) prior to presentation [11,12]. History of pica may be present [9].

In EHPVO, a bimodal age of presentation has been described – those secondary to UVC or umbilical sepsis usually manifest early (~3 years) whereas those following intra-abdominal infections or idiopathic ones manifest late (~8 years) or sometimes into early adulthood [4,43]. Mean ages of first bleeding episode and initial presentation are 5.3 years and 6.3–9.3 years, respectively, with a mean number of 1.8–3.1 bleeding episodes per child before presentation [31,40,68–74]. Episodes of variceal bleed are recurrent, mostly related to febrile illnesses, are more frequent and severe with increasing age of onset, but recurrences tend to decrease after puberty. Splenic size and portal pressure do not correlate with the incidence or severity of bleed [4].

Hypersplenism, mostly asymptomatic, is present in both the disorders especially in older children or young adults. Bleeding from non-gastrointestinal sites is reported in about 20% [13]. Ascites develops in 10–34% of NCPF and 13–21% of EHPVO cases usually after a bleeding episode and is related to hypoalbumine-

mia, and prolonged duration of PHT with subsequent progressive deterioration of liver functions [4–13,75]. Other common presentations are repeated attacks of left upper quadrant pain due to perisplenitis or splenic infarction [2]. Mesenteric vein thrombosis, bowel ischemia, hemoperitoneum, hemobilia, and pulmonary emboli are rarely seen [57].

On clinical examination, both the disorders have moderate to massive splenomegaly (average size 11 cm below costal margin). In NCPF/IPH, liver may be normal, enlarged or slightly shrunken, whereas in EHPVO, it is normal or shrunken. Peripheral stigmata of chronic liver disease are absent. Jaundice and hepatic encephalopathy are rare (~2%) in NCPF/IPH and usually seen either after a major bleed or shunt surgery [11]. In EHPVO, jaundice develops secondary to development of portal biliopathy.

Laboratory findings

Hypersplenism is seen in 27–87% with anemia being the commonest abnormality followed by thrombocytopenia and leucopenia. Anemia is usually microcytic hypochromic and is related to multiple variceal bleeds, hypersplenism and iron deficiency [10–13]. In NCPF/IPH, liver function tests are mostly normal, but derangements in liver enzymes, prothrombin time and albumin are seen in a small proportion [9–15] (Table 3). Similarly, in EHPVO, elevations of alkaline phosphatase and gamma-glutamyl transpeptidase are seen with development of portal biliopathy, and hypoalbuminemia may be seen during bleed episodes [4]. Hypoxemia secondary to intrapulmonary vascular dilations may be seen [4]. Frequencies of hepatitis B and C infections are comparable to that in the general population, but are higher in transfused patients from remote areas [4,12]. In EHPVO, splenic stiffness is high and a value above 42.8 kPa predicts variceal bleed with fairly good accuracy [76].

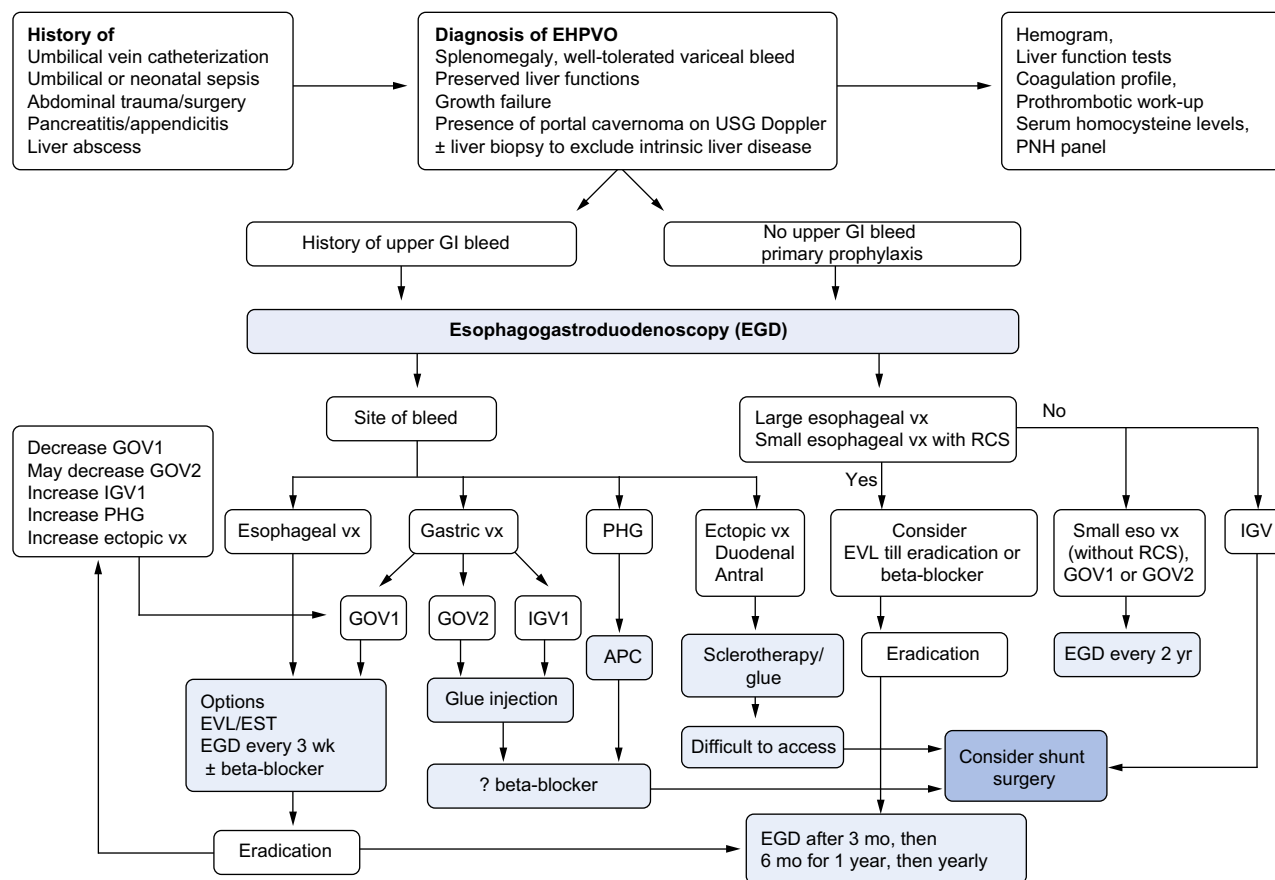


Fig. 4. Algorithmic approach for the diagnosis of EHPVO and management of esophageal and gastric varices. APC, Argon plasma coagulation; EST, endoscopic sclerotherapy; EVL, endoscopic variceal ligation; GOV, gastroesophageal varices; IGV, isolated gastric varices; PHG, portal hypertensive gastropathy; PNH, paroxysmal nocturnal hemoglobinuria; RCS, red colour signs; Vx, varix.

Coagulation and platelet abnormalities

Prolonged prothrombin time, reduced fibrinogen and reduced platelet aggregation is seen in around 80% of NCPF/IPH and EHPVO cases, despite their association with prothrombotic disorders. In addition, patients with EHPVO have a state of low grade disseminated intravascular coagulation secondary to portosystemic shunting [77]. The activity of ADAMTS13 (disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), a zinc-containing metalloprotease, which cleaves the von Willebrand factor, is significantly reduced in patients with NCPF/IPH [78].

Hemodynamics

Intra-splenic (ISP) and intra-variceal pressures (IVP) are significantly elevated in both NCPF/IPH as well as EHPVO as compared to wedge hepatic venous pressures (WHVP) and intrahepatic pressures (IHP), suggesting a presinusoidal level of block. In NCPF, two patho-anatomic sites of resistance have been demonstrated (Fig. 3). HVPG is normal in EHPVO, whereas it is normal or slightly elevated in NCPF (median 7 mmHg). IVP is the investigative tool of choice for PHT in both entities. Among bleeders, IVP is comparable in those with cirrhosis and EHPVO, but at a given value, cirrhotics are more likely to bleed than EHPVO. In addition, in EHPVO, hepatic blood flow is normal or decreased, depending on collateral flow and hepatic arterial buffer response [2,79].

Hyperdynamic circulatory state has been demonstrated in both of these disorders [80].

Autonomic dysfunction

Autonomic dysfunction, again secondary to hyperdynamic state and elevated nitric oxide levels, is present in 25% and 67% of NCPF/IPH and EHPO cases, respectively [81,82]. Reduced alpha-adrenergic vasoresponsiveness in a rabbit model of NCPF/IPH has been demonstrated, a finding comparable to cirrhotic PHT [83].

Immunological alterations

In NCPF/IPH, total peripheral T lymphocytes and suppressor/cytotoxic phenotype [T8] cells are reduced and the ratio of T4–T8 cells is significantly increased [84]. Vascular cell adhesion molecule-1 and soluble tumor necrosis factor (TNF)-receptor I and II are increased in the blood without any significant increase of TNF. Despite heightened Th1 response, cellular infiltration is not so remarkable [85]. Endothelin-1 levels are increased in splenic B lymphocytes, periportal hepatocytes, portal venules, and hepatic sinusoids [86]. Levels of connective tissue growth factor, which stimulates *in vitro* fibroblast proliferation and synthesis of extracellular matrix, are increased [87]. Mixed autologous lymphocytic reaction is defective [88]. It remains to be established, whether these immunological anomalies are a result or the cause of NCPF/IPH. Similarly, in EHPVO, predominantly there are abnormalities of cell-mediated immunity, whereas humoral immunity

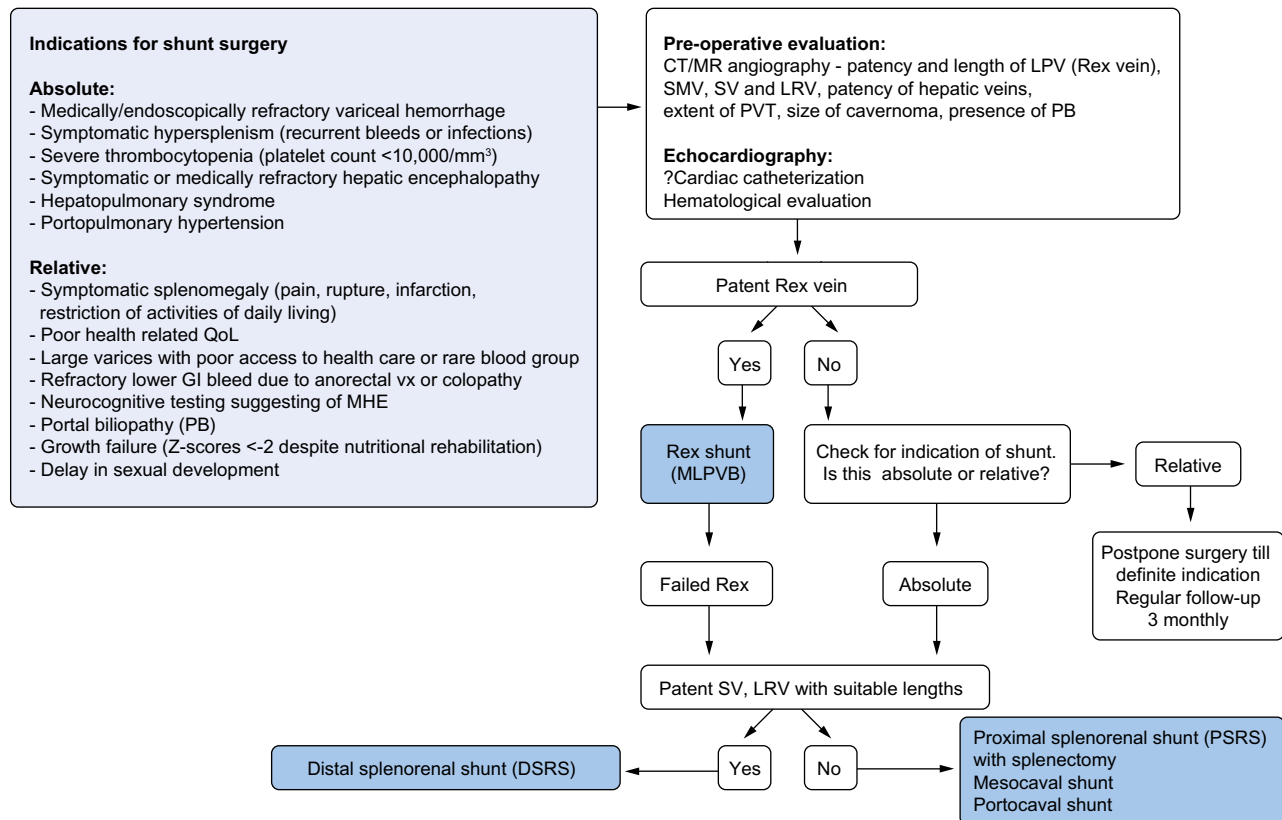


Fig. 5. Surgical considerations in EHPVO. Pre-operative assessments include those by adult and/or pediatric hepatologist (for growth and to decide timing of surgery and need for liver biopsy to exclude intrinsic liver disease), cardiologist (echocardiography with or without cardiac catheterization, to exclude HPS and portopulmonary hypertension), hematologist (for prothrombotic states) and radiologist (CT and MR angiography with or without portography to indicate patency and length of LPV, SMV, SV, and LRV; patency of hepatic veins, extent of thrombus, size of cavernoma and presence of biliopathy). For absolute indications and patent LPV, Rex-shunt or MLPVB is the procedure of choice. When the indications of surgery are relative and intrahepatic, LPV could not be assessed preoperatively, then one should not proceed to DSRS directly and surgery should be delayed until there are absolute indications. LPV, left branch of PV; LRV, left renal vein; SMV, superior mesenteric vein; SV, splenic vein.

is well preserved. This is explainable by splenic sequestration of T cells and presence in serum of factors influencing the kinetics of lymphocyte response [4].

Endoscopic findings

Esophageal varices are seen in 80–90% of NCPF/IPH and EHPVO cases [12,89] (Table 4). In comparison to cirrhotics, esophageal varices are more often large (90% vs. 70%), gastroesophageal varices (GOV1 and GOV2) more common (31–44% vs. 22%), portal hypertensive gastropathy (PHG) less common (10.9% vs. 5.4%), and anorectal varices larger and more common (89% vs. 56%) [89,90]. Isolated gastric varices (IGV1) are present in around 6% of EHPVO patients and IGV2, indicative of ectopic or duodenal varices, are also common in these patients [89]. PHG develops usually after variceal eradication and is often transient, non-progressive and asymptomatic [90]. On initial endoscopy, if esophageal varices are small, one should look for gastric varix or spontaneous shunt [17]. In EHPVO, anorectal varices and colopathy are seen in 63–95% and 54% of cases, respectively – possibly related to selective redistribution of portal pressure to inferior mesenteric vein. Bleeding from them, although rare (0.5–10%), may be torrential and life-threatening [91,92].

Radiological features

Doppler USG is the first line radiological investigation in both disorders. In NCPF/IPH, liver is normal in size and echotexture. Spleen is enlarged with presence of gamma-gandy bodies; splenoportal axis is dilated and patent in NCPF/IPH. PV is thickened (>3 mm) with echogenic walls and its intrahepatic radicles are smooth and regular. There is sudden narrowing or cut-off of intrahepatic second and third degree PV branches – “withered tree” appearance along with approximation of vascular channels. Splenic index and PV inflow are high [10,11]. Spontaneous shunts (paraumbilical and gastroadrenorenal) are seen in 16% [11]. Intrahepatic PV abnormalities (non-visualization, reduced caliber and perfusion defects are certain features on contrast-enhanced computed tomography (CT), which help in differentiating NCPF/IPH from cirrhosis [93]. Radionuclide scintigraphy using ^{99m}Tc-Sn colloid shows absence of increased bone marrow uptake [8].

For the diagnosis of EHPVO, Doppler USG of SPA has a sensitivity and specificity above 95% [4]. There is cavernomatous transformation of PV. Splenoportography or arterial portography have been replaced by non-invasive methods – CT and magnetic resonance (MR) angiography and portography, which besides providing diagnosis also give anatomical road-map prior to shunt surgery [94].

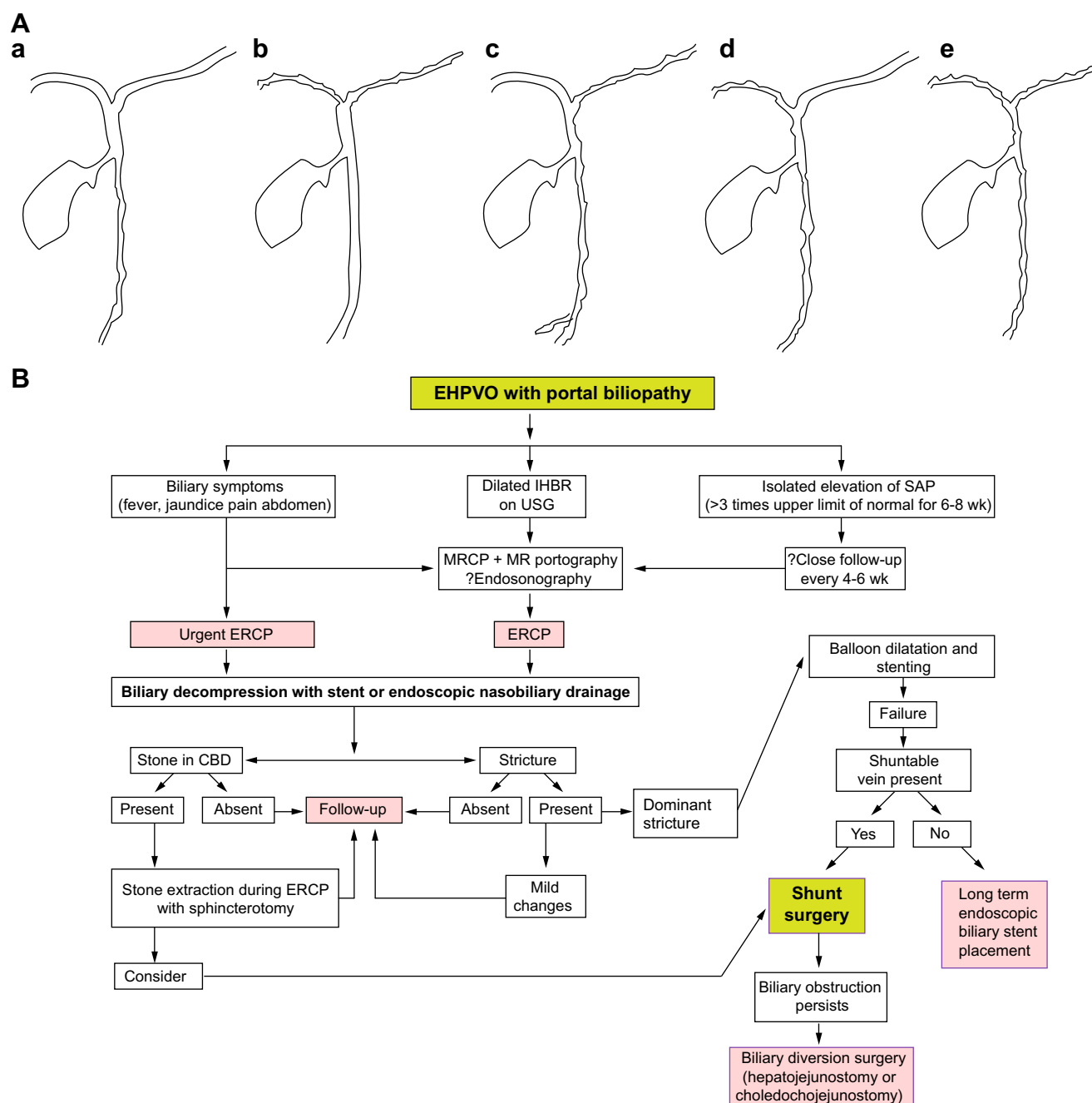


Fig. 6. Portal biliopathy. (A) Classification of cholangiographic abnormalities in Portal biliopathy. On the basis of location and extent of abnormalities, changes are classified as Type I: Involvement of only extrahepatic bile duct (a); Type II: Involvement of only intrahepatic bile duct (b); Type III a: Involvement of extrahepatic and unilateral (right or left) intrahepatic bile duct (c and d); and Type III b: Involvement of extrahepatic and bilateral intrahepatic ducts (e) [109]. (B) Algorithm for management of biliopathy in EHPVO. Asymptomatic portal biliopathy needs regular follow-up with liver function tests and does not require any treatment. Symptomatic biliopathy is a definite indication for intervention – endoscopic or surgical. Endoscopic interventions include sphincterotomy, stone extraction, biliary stenting, stricture dilatation and mechanical lithotripsy [109]. If the biliary obstruction remains unrelieved after endotherapy, porto-systemic shunting is required as a definitive procedure. In those cases, where biliary obstruction persists after surgery, a second stage hepatojejunostomy may be needed; the second procedure is usually facilitated by the first one due to disappearance of cavernoma and better visualization of operative field. Symptomatic biliopathy is one of the few indications where portosystemic shunting is considered even in the absence of variceal bleeding [138–141]. CBD, common bile duct; IHBR, intrahepatic biliary radicles; SAP, serum alkaline phosphatase.

Liver biopsy

Liver biopsy is not essential for the diagnosis of EHPVO unless the underlying chronic liver disease is suspected, but it is indicated in NCPF/IPH to exclude cirrhosis and other etiologies of PHT [17,33].

Hillaire *et al.* have considered 4 pathological findings for diagnosis of NCPF/IPH – hepatoportal sclerosis, periportal fibrosis, perisinusoidal fibrosis and nodular regenerative hyperplasia [14]. Diagnosis on liver biopsy is based on a specimen longer than 1 cm with >5 complete portal tracts (CPT) along with alternation

Table 5. Endoscopic outcomes in patients with EHPVO.

| Study (yr) [Ref.] | No. of subjects (endotherapy) | FU interval | Erad of eso vx | No. of sessions | Effect | Recurrence | | Change in GVx | Change in PHG | Mortality | Complications |
|---|-------------------------------|--------------------------|----------------|----------------------------|--|-------------------|----------------|---|------------------------------|-------------------------|---|
| | | | | | | Bleed | Eso vx | | | | |
| Studies on long-term efficacy of EST | | | | | | | | | | | |
| Yachha (1997) [123] | 50 (EST) | 19 ± 4 mo | 88% | Mean 8 | Reduction in risk of bleed 0.2/mo to nil | 26% | 10% | 40% to 70% | n.a. | 0% | n.a. |
| Zargar (2004) [69] | 69 (EST) | Median 3 yr | 91% | 6.3 ± 1.8 | Reduction in bleed 0.860 → 0.028 patient-yr | 12% | 14% | n.a. | n.a. | 1.4% | Esophageal ulcers 13% Strictures 4% Aspiration 3% |
| Itha (2006) [71] | 183 (EST) | 3.1 ± 1.8 yr | 89% | 7.7 ± 1.8 | Reduction in GOV1, Increase in GOV2, IGV and PHG | 7% (all from GVx) | 40% | GOV1 50 to 34%; GOV2 9 to 14%; IGV 1 to 9% | 12 to 41% (severe 0.6 to 7%) | 0% | n.a. |
| Poddar (2008) [31] | 278 (EST) | 34 ± 28 mo | 95% | 5 ± 2.4 | - | 3% | 14% | n.a. | n.a. | 1.7% | Esophageal ulcers 16% Strictures 17% Perforation 2% |
| Thomas (2009) [72] | 198 (EST) | Median 20 yr | n.a. | n.a. | Recurrence of bleed in mean 5.4 yr, Decrease in GOV, Increase in PHG and GVx | 17% | 20% | GOV1 19 to 2.5%, GOV2 13 to 11%, IGV1 same | 23 to 29% (severe 9 to 11%) | 1.5% (unrelated to EST) | Esophageal stricture 14.6% |
| Studies on EVL vs. EST | | | | | | | | | | | |
| Sarin SK (1997) [124] | 48 (EST) 47 (EVL) | n.a. | n.a. | 5.2 ± 1.8 vs. 4.1 ± 1.2 | Faster cure, lesser sessions, less stricture, PHG and rebleed with EVL | 21% vs. 6%* | 8% vs. 29%* | GOV1 obliteration 52% vs. 59% | New PHG 20% vs. 2%* | 6% vs. 6% | Stricture 10% vs. 0%* |
| Zargar (2002) [68] | 24 (EST) 25 (EVL) | Mean 22 mo | 92% 96% | 6.1 ± 1.7 3.9 ± 1.1* | EST has more complications, early cure with EVL | 25% 4%* | 10% 17% | n.a. | n.a. | 0% 0% | 25% vs. 4%* |
| Studies on effect of EST and esophageal variceal eradication on PHG and gastric varices | | | | | | | | | | | |
| Yachha (1996) [122] | 40 (EST) | n.a. | n.a. | n.a. | Increase in PHG | n.a. | n.a. | n.a. | 40 to 80% (severe 0 to 50%) | n.a. | n.a. |
| Poddar (2004) [70] | 274 (EST) | 38 ± 30 mo | 95% | 4.5 ± 1.9 | Reduction in GOV, Increase in IGV and PHG | 3% | 4.3% | GOV 64 to 45% IGV 1 to 14% | 25% to 52% (severe 3 to 16%) | 2% | n.a. |
| Studies on EVL followed by EST vs. EST | | | | | | | | | | | |
| Poddar (2011) [74] | 101 (EVL to EST) 60 (EST) | 33 ± 18 mo 43 ± 17 mo | 100% 95% | 5.2 ± 1.8 6.8 ± 2.8* | Early cure, less complications with EVL followed by EST | 4% 10% | 26% 39% | GOV1 52 to 30%; GOV2 9 to 22%; IGV 3 to 11% | 16 to 58% | n.a. | 7% 28% |

Erad, eradication; Eso, esophageal; FU, follow-up; GOV, gastroesophageal varix; GVx, gastric varix; IGV, isolated gastric varix; n.a., not available; RCT, randomized controlled trial.

*Indicates significant difference with $p < 0.05$.

of CPT and central veins to exclude cirrhosis; and more than 2/3 (66%) of CPTs should have absence or reduced caliber portal venules with sclerosis or thickening of smooth muscle wall [15].

HIV and NCPF/IPH

NCPF/IPH in the setting of HIV and AIDS needs special mention [21,95,99]. The prevalence of NCPF/IPH in HIV is around 0.45–1% and is rapidly increasing. This is due to prolonged survival of HIV infected patients following usage of highly active antiretroviral therapy (HAART) and is related to either one or a combination of the following factors – recurrent opportunistic gut infections, usage of HAART especially didanosine, hypercoagulability, direct effect of HIV – but the exact mechanism still remains unclear [21,95,99]. The role of the underlying prothrombotic state is controversial [21,96,97]. HIV virus itself may be implicated in the disease pathogenesis as indicated by its propensity to infect hepatic stellate cells and cause endothelial injury via cytokines like endothelin-1, interleukins-1 and 6 and platelet derived growth factor [99]. HIV related NCPF occurs predominantly in males (50–100%), homosexuals (50–75%), prolonged infection (median 11.5 years, range 7–15 years) and is associated with immune reconstitution. Patients with HIV who develop NCPF are older with reduced platelets and CD4 counts, elevated liver enzymes, and have longer exposure to didanosine or concomitant exposure to stavudine or tenofovir [21,95–98]. Presentation is with features of PHT. Median liver stiffness is 7.8–10.2 kPa. Median HVPG is 8 mmHg. PVT has been observed in 25–75% [95,96]. Liver decompensation requiring liver transplantation (LTx) has been reported [100].

Management of NCPF and EHPVO

The natural course of NCPF/IPH is usually simple, except for development of PVT and hepatopulmonary syndrome (HPS) in a few of them, whereas in EHPVO the natural history is more complex because of early insult and is compounded by presence of growth failure, very slow but progressive parenchymal extinction, impaired quality of life (QoL), minimal hepatic encephalopathy (MHE) and portal biliopathy (Figs. 4–6).

Natural history and prognosis of NCPF

Long term survival after eradication of esophagogastric varices and after a properly timed shunt surgery is nearly 100% and 80%, respectively [17,101]. Liver functions usually remain well preserved, but with course of time in 20–33% of cases, liver slowly undergoes parenchymal atrophy with subsequent decompensation, development of HPS and need for LTx [102,103]. Uncontrolled variceal bleeding is a common cause of death [17]. In a French follow-up study, PVT, ascites and liver failure have been shown to develop in 46%, 50%, and 21%, respectively, over a mean period of 7.6 years – the later 2 complications were associated with variceal bleeding, surgery or concurrent extrahepatic disease [14]. Worsening of preexisting PHT and development of new PVT occurred in 46% and 28%, respectively, with a proportion requiring LTx [15]. Development of PVT is thus considered a major event contributing to progression of liver disease and eventual decompensation. However, the same has not been shown in the transplant and autopsy series [102,103].

Natural history and prognosis of EHPVO

While the overall prognosis of EHPVO after control of variceal bleed is good, with long term (>10 years) survival nearly 100% [4], there are certain issues which need to be addressed.

Growth retardation

Stunting and wasting is present in 37–54% and 31–57% of children with EHPVO, respectively. Growth depends on duration of PHT and declines further on follow-up despite appropriate energy intake [104–107]. Impaired growth is possibly related to one or more factors – (i) reduced portal blood supply to liver and deprivation of hepatotropic factors [4]; (ii) poor substrate utilization and/or malabsorption due to portal hypertensive enteropathy, supported by studies demonstrating improvement in growth indices after portosystemic shunt surgery [107]; (iii) growth hormone (GH) resistance, evidenced by high levels of GH and low levels of insulin-like growth factor-1 (IGF-1) and IGF binding protein-3 (IGFBP-3) [105–107] and (iv) anemia and hypersplenism.

Impaired quality of life (QoL)

Children with EHPVO have poor health-related QoL with lower median scores in physical, social, emotional, and school functioning health domains as compared to controls. These scores are unaffected by esophageal eradication and show improving trend after shunt surgery [107,108].

Portal biliopathy

Portal biliopathy refers to biliary ductal (extra- and intra-hepatic) and gall-bladder wall abnormalities in patients with PHT, which take the form of intrahepatic biliary radicles dilatation, indentations, caliber irregularities, displacements, angulations, ectasias, strictures, common bile duct stones, filling defects, compressions, gall-bladder, and pericholedochal varices or a mass (pseudocholangiocarcinoma sign). Frequency of these changes in patients with EHPVO, cirrhosis and NCPF is 80–100%, 0–33%, and 9–40%, respectively. Increased prevalence of biliopathy in EHPVO is related to long standing portal cavernoma in the biliary and peribiliary region, causing compressive and ischemic changes on the biliary tree, the later ones may remain irreversible even after shunt surgery [109]. The left hepatic duct is involved more commonly (38–100%) and severely. Liver histology is essentially normal. Portal biliopathy usually remains asymptomatic (62–95%). Common symptoms are jaundice, biliary colic, abdominal pain and recurrent cholangitis and are seen with old age, long-standing disease, presence of stones and abnormal liver function tests [109–113]. ERCP is the diagnostic gold standard, but, being invasive is indicated in symptomatic cases requiring endotherapy. A classification based on ERCP has been proposed (Fig. 6A) [109]. MRCP with portography has equal efficacy and is also helpful in differentiating choledochal varices from stones. Radiologically, biliopathy commonly occurs in those EHPVO cases, where PVT extends into mesenteric veins or bile duct is more acutely angulated (median 110° vs. 128°) [114]. Natural history of biliopathy is ill-defined and varies from asymptomatic state to development of various sequelae like choledocholithiasis, cholangitis, and secondary biliary cirrhosis. About 4–10% of portal biliopathy cases may succumb to these sequelae despite endoscopic treatments [109,111].

Table 6. Surgical outcomes in patients with EHPVO.

| Study (yr) No. of subjects | Type of surgery/intervention | Indications | FU interval | Rebleed | Success or patency of shunt | HE or MHE | Conclusions | Mortality |
|--|---|---|--------------|-------------------------------|-----------------------------|-----------------------------------|---|---------------------------|
| Bismuth (1980) n = 52 [128] | PSRS, MCS, DSRS, PCS | n.a. | 4 yr | 2% | 94% | 0% | - | 0% |
| Alvarez (1983) n = 76 [129] | PSRS, MCS | 64 VB 12 prophylactic | Mean 43 mo | 8% | 92% | 0% | Resolution of bleeding and improvement in growth in 100% | 0% |
| Warren (1988) n = 70 [130] | 10 Splenectomy 10 Devascularization 25 DSRS 6 Other shunts 12 EST | VB | n.a. | 4% 50% 4% 67% 28% | - - 96% 17% - | n.a. n.a. 0% 17% n.a. | Following DSRS, significant increase in liver blood flow and platelet count (99 to 183 x 10 ³ /mm ³ , decrease in spleen volume (905 cc to 337 cc at 4.5 yr) | 20% 30% 27% |
| Gauthier (1989) n = 59 [131] | PSRS, MCS, PCS, H-Type | n.a. | Mean 12 mo | 7% | 92% | 0% | H-type shunts successful overall in 95% cases; 50% of failed initial shunts managed with H-type shunts | n.a. |
| Mitra (1993) n = 81 [132] | LRS without splenectomy | * | Mean 54 mo | 10% | 84% | 0% | Improvement in growth, shunt patency correlated with disappearance of vx, reduction in spleen size and splenic pulp pressure and improvement of hypersplenism | n.a. |
| Prasad (1994) n = 160 [133] | PSRS | n.a. | 12-156 mo | 11% | n.a. | 0% | 15-yr survival 95%; pneumococcal meningitis in 1 (0.6%), recurrent malaria in 24% | 4% |
| Orloff (1994) n = 162 [51] | PSRS, MCS | Failed EST (49%) or surgery (26%) | 5-35 yr | 2% | 98% | 0% | 5- and 10-yr survivals 99% and 96% Improvement in QoL and social functioning | 1.9% |
| Menon (2005) n = 30 [107] | PSRS, LRS, Devascularization | n.a. | 1-4 yr | n.a. | 100% | n.a. | Improvement in WZS in 50% and HZS in 76% Improved school performance in 85% Personality improvement in 73% | 0% |
| Wani (2011) n = 61 [73] | 31 Surgery (RCT) 31 EST | VB VB | n.a. n.a. | 3% 23% | 97% | n.a. | Less re-bleeding episodes and lesser transfusions in surgery group | 3% 3% |
| Studies on Rex shunt (mesenterico-left portal vein bypass, MLPVB) | | | | | | | | |
| Stringer (2007) n = 11 [134] | Rex | n.a. | n.a. | 0% | 100% | n.a. | BMIZS improved from -0.44 to +0.46 | 0% |
| Lautz (2009) n = 45 [135] | Rex | n.a. | 5-24 mo | 0% | 100% | n.a. | Improvement in WZS from -0.49 to +0.35, HZS from -0.42 to -0.14 and BMIZS from -0.22 to +0.48 | 0% |
| Superina (2006) n = 34 [136] | Rex | 22 VB, 11 Splenomegaly, 1 HE following shunt | 1-7 yr | 0% | 91% | 0% | Increase in plts (54 to 160 x 10 ³ /mm ³), WBC (2600 to 4600/mm ³), decrease in spleen size (11 cm to 3 cm BCM) and PT (16.6 to 13.7 s), increase in SMV flow, LPV diameter and liver volume | 0% |
| Mack (2006) n = 12 [137] | 9 Rex 3 DSRS | n.a. | 1 yr | n.a. n.a. | 89% 100% | 0% 0% | Improvement in fluid neurocognitive ability with patent Rex shunt vs. non-patent Rex and DSRS | 0% |
| Chaves (2012) n = 92 [94] | Rex | n.a. | n.a. | n.a. | 75% | n.a. | Pre- and post-operative CT/MR helps in diagnosing patency and size of LRV and SMV, shunt stenosis or occlusion | 0% |

| Study (yr) No. of subjects | Type of surgery/intervention | Indications | FU interval | Rebleed | Success or patency of shunt | HE or MHE | Conclusions | Mortality |
|--|--|------------------------|-------------|---------|-----------------------------|-----------|--|-----------|
| Surgery in Portal biliopathy (PB) | | | | | | | | |
| Chaudhary (1998) n = 9 [138] | 2 CJ 7 PSRS + splenectomy | Symp PB | n.a. | n.a. | 0% 71% | n.a. | 2 (29%) with PSRS with bile duct stricture required second stage HJ; 2 more with CBD stone required ERCP intervention | 50% 0% |
| Oo YH (2009) n = 13 [139] | 6 ERCP 1 MCS; 2 TIPSS 3 spontaneous resolution 1 unresolved | Symp PB Failed ERCP | 1-18 yr | 77% | - | n.a. | Endoscopic management is effective initial therapy for symptomatic PHB. For persistent symptoms, shunt surgery should be considered | 15% |
| Chattopadhyay (2012) n = 56 [140] | 40 PSRS 16 splenectomy + devascularization | Symp PB | n.a. | n.a. | 88% | n.a. | Overall PHB reversed in 88%, Bilirubin decreased in both groups, 15% required biliary decompression procedures | n.a. |
| Agarwal (2011) n = 37 [141] | PSRS | Symp PB | Mean 32 mo | 0% | 97% | n.a. | Second stage surgery required in 13 (35%); 11 HJ, 1 CJ, 1 CCx | 0% |

* >1 major variceal bleed, severe hypersplenism, fundal vx, rare blood group, remote location, non-compliance to EST; BCM, below costal margin; BMISZ, BMI Z-score; CBD, common bile duct; CCx, cholecystectomy; CJ, cholecystojejunostomy; FU, follow-up; HE, hepatic encephalopathy; HJ, hepatojejunostomy; HZS, height Z-score; LRS, leiorenal shunt; LRV, left renal vein; MCS, mesocaval shunt; mo, months; n.a., not available; PCS, portocaval shunt; Plts, platelets; PT, prothrombin time; RCT, randomized controlled trial; SMV, superior mesenteric vein; Symp, symptomatic; TIPSS, transjugular intrahepatic portosystemic stent shunt; VB, variceal bleed; WBC, white blood cells; WZS, weight Z-score; yr, years.

Minimal hepatic encephalopathy (MHE)

MHE has been described in the setting of EHPVO with or without shunt surgery [115–118]. Post-shunt surgery, there is direct entry of toxic substances from portal blood into systemic circulation bypassing the liver; prevalence is more with non-selective as compared to selective shunts. MHE has also been reported in 32–35% of EHPVO cases without surgical shunt on the basis of abnormalities in critical flicker frequency, psychometric tests and P300 auditory event-related potential [115]. MHE in EHPVO is associated with presence of spontaneous shunts, elevated brain glutamine and glutamine/creatine ratio on ¹H-MR spectroscopy, high blood ammonia and proinflammatory cytokines (tumour necrosis factor- α and IL-6), increased mean diffusivity on diffusion tensor imaging in several areas of the brain, suggesting a role of hyperammonemia and inflammation in its pathogenesis [116,117]. Post shunt surgery, there is further increase in the incidence of MHE along with ammonia and glutamine/creatine ratio; associated with decrease in brain myoinositol [118]. MHE persists in 75% and new onset MHE develops in 5% over 1 year [119]. Usage of lactulose improves MHE in 53% [120].

Liver dysfunction

Progressive deterioration of liver functions and ascites may develop with increasing age, prolonged duration of disease and development of portal biliopathy. Such patients generally have reduced hepatic cell mass and synthetic dysfunction [75].

Management

Management in both NCPF/IPH and EHPVO is primarily focused on management of an acute episode of variceal bleeding followed by secondary prophylaxis. Other areas deserving attention are splenomegaly, hypersplenism, growth, portal biliopathy and MHE, the last three especially in EHPVO. The management of EHPVO needs to be individualized depending on the age of presentation, site and nature of obstruction, and clinical manifestations. Figs. 4–6 show algorithmic management of EHPVO.

Control and prophylaxis of variceal bleed

Variceal bleeding is a severe complication in both NCPF/IPH and EHPVO. In view of limited data on usage of vasoactive drugs, propranolol, endotherapy and shunt surgery in these 2 conditions, Baveno V consensus has recommended that the same principles can be applied [34].

Medical management

Vasoactive drugs, such as somatostatin, octreotide, or terlipressin, should be started early. A single randomized controlled trial (RCT) in NCPH from our group has shown equal efficacy of propranolol and endoscopic variceal ligation (EVL) for prevention of rebleeding – 47% showed reduction in grade of varices and 18% had minor adverse effects in the propranolol group [121].

Endoscopic variceal obliteration

Endoscopic sclerotherapy (EST) and EVL are effective in 80–90% of patients in controlling acute bleeding from esophageal varices and preventing rebleeding. Endotherapy is more effective with less rebleeding rates when combined with vasoactive drugs.

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EST and EVL have comparable efficacy for eradication of varices. However, EVL as compared to EST eradicates varices faster, with lesser complications and rebleed rates, but with increased rate of variceal recurrence [68–74,122–124] (Table 5). For GOV2 or IGV1 related bleed, glue injection with N-butyl-cyanoacrylate is helpful. Endotherapy should be repeated at 2–3 weekly intervals until variceal eradication [17,34] (Fig. 4).

Surgical management

Surgery is primarily indicated in patients with variceal bleed who fail to respond to endoscopic management [33,125]. Other indications are mentioned in Fig. 5. Various types of surgical procedures are:

- (i) *Shunt/Bypass procedures*: Non-physiological shunts bypass the portal blood either totally or partially into systemic circulation. Total and partial shunts are also known as non-selective and selective shunts, respectively, as the later selectively decompress the gastrosplenic zone. Physiological shunts, like mesenterico-left PV bypass (MLPVB) or Rex shunt, maintain the hepatic portal blood flow, while bypassing the level of obstruction. It decompresses the splanchnic bed from the superior mesenteric vein to the left branch of PV via an autologous graft (usually internal jugular vein).

There are many long-term surgical series on EHPVO, although the data on NCPF/IPH is limited (Table 6) [51,126–137]. In NCPF/IPH, following shunt surgery, esophageal varices, splenic size and splenic pulp pressure reduce [126], but there is risk of MHE, glomerulonephritis, pulmonary arteriovenous fistula and ascites [127]. In EHPVO, technical difficulty, shunt thrombosis, rebleeding and MHE are concerns. Improvement in surgical techniques has largely tackled these issues. Selective shunts like distal splenorenal shunt (DSRS) are superior to non-selective ones like central (CSRS) or proximal splenorenal shunts (PSRS) in terms of patency and lower rebleeding and encephalopathy rates [4,33]. Physiological shunts actually cure the disease or defect, and not only the symptoms and sequelae of PHT. Post-Rex shunt, there is improvement in coagulation status, growth indices and liver volume, reduction of spleen size, correction of hypersplenism, reversal of hepatic encephalopathy and improvement in fluid neurocognitive ability in the form of attention span, processing speed and short-term memory. MLPVB also prevents development of portal biliopathy and liver disease in adulthood. For these reasons, MLPVB has become the initial procedure of choice in EHPVO cases [134–137] (Table 6). Minimum age of 8 years and shuntable vein size of 6.5 mm were initially advocated for non-selective shunts, but for MLPVB, minimum reported age is 1 month, and a vein size of 2 mm is considered adequate [137].

There is limited data to recommend shunt surgery over endoscopic therapy or vice versa. In a single RCT from India, comparable mortality and treatment failure has been shown in both, but with higher rebleeding and blood transfusion requirement with EST [73]. However, most experts feel that if there are shuntable veins and the requisite surgical expertise is available, it is better to do shunt surgery in patients with EHPVO. This helps in growth recovery and may reduce the development of gastric and ectopic varices and worsening of portal biliopathy [4,33,125].

- (ii) *Ablative procedures*: These include esophagogastric devascularization alone or in combination with splenectomy and are done in patients with failed shunts, those without any shuntable veins, or in emergency situations with refractory variceal bleed. In view of high rebleeding rates and mortality, these procedures have become obsolete [4].

Failure of endoscopic therapy

In 8–12% of cases endotherapy may fail to control acute variceal bleed. In emergency scenarios surgical ablative procedures, transjugular intrahepatic portosystemic shunt (TIPSS), or balloon-occluded retrograde transvenous obliteration (BRTO) can be done – decisions of which remain individualized [33,34].

Anticoagulation

In both NCPF/IPH and EHPVO, there is no consensus on the role or indication of anticoagulation therapy. However, in a known prothrombotic state, this should be considered to prevent recurrent thrombosis.

Portal biliopathy

It is one of the serious manifestations of long standing EHPVO. The management is generally supportive and not curative as the portal cavernoma and PHT continue to compress and afflict the adjoining biliary system. A comprehensive algorithmic approach for the management of biliopathy is given in Fig. 6B [109,110,138–141].

Follow-up

It is recommended that NCPF/IPH cases should be followed-up at 6 monthly intervals for clinical and laboratory evaluation, close surveillance for evidence of decompensation and development of PVT, HPS and biliopathy. EHPVO children need 3 monthly follow-up for growth monitoring, spleen size, QoL, school performance, learning abilities, evidence of biliopathy. Endoscopic surveillance is needed following variceal eradication after every 3–6 months, and in non-bleeders with large and small varices after every 6 and 12 months, respectively.

Miscellaneous causes of NCPH

Apart from NCPF/IPH and EHPVO, there are numerous other causes of NCPH with a similar presentation. Three of the common ones have been discussed underneath.

Hepatic schistosomiasis

Liver involvement due to schistosomiasis occurs due to one of the two trematode flukes – *Schistosoma mansoni* and *japonicum*. While the former is seen predominantly in Africa and South America, the latter is common in eastern Asia, especially mainland China. The larval forms of the former reside in colonic and rectal tributaries, whereas those of the later reside in the superior mesenteric vein. Liver disease develops secondary to entrapment of eggs in portal venules (<50 mm in diameter) with granulomatous inflammation leading to fibrosis (termed “Symmers pipe-

stem fibrosis") in 4–8% of cases and subsequent presinusoidal PHT [142]. Inflammatory response elicited by live eggs is initially of Th1 type with intense granulomatous inflammation, but later on this is substituted by Th2 response with development of fibrosis [143]. Deposition of procollagens I, III and IV, as well as its markers (fibronectin and glycosaminoglycans) is increased – this is positively regulated by interleukin (IL)-13 and negatively by gamma-interferon [143,144]. In schistosomal mice models, it has been demonstrated that various proteins related to stress, immunity, anti-oxidative response and structural components are increased, while those related to various metabolic cycles are decreased [143]. The *Foxp3* gene, necessary for generation of CD4+ CD25+ T reg cells, is overexpressed and ameliorates granuloma formation in such livers [145]. Severe disease is associated with the HLA-A5 allele and a gene closely linked to interferon-gamma receptor [142].

Clinical presentation is similar to NCPF and EHPVO. Diagnosis is based on demonstration of eggs in stools or rectal biopsy. Stool microscopy is performed by Kato-Katz method. Serological tests for diagnosis are enzyme-linked immunosorbent assay with soluble antigen of *Schistosoma mansoni* eggs using sodium metaperiodate (ELISA-SEA-SMP), alkaline phosphatase immunoassay (APIA) and the circumoval precipitin test (COPT) [146]. Sonographically, there is echogenic thickening along PV radicles, and septae giving a fish-scale network appearance. CT scan shows capsular and septal calcifications, irregular hepatic contour, junctional notches, and hypoattenuating bands or rings around the portal tracts producing a turtle back appearance [142].

Natural history of PHT is closely related to the number of eggs deposited in the liver, which roughly parallels the number of eggs excreted in stool of untreated patients. PHT is initially presinusoidal and gradually becomes perisinusoidal [142]. Treatment with praziquantel leads to complete regression of periportal thickening in 28.2% of cases within 3–5 years, followed by reduction in size of spleen, and diameter of mesenteric and splenic veins [146]. A recent metaanalysis has shown superiority of a combination of artemesinin and praziquantel over praziquantel alone [147]. Management of PHT is by endotherapy, beta-blockers or surgery. Esophagogastric devascularization with splenectomy has been shown to improve hyperdynamic circulatory state with lesser mortality and complications rates than DSRS in schistosomiasis patients [148,149].

Congenital hepatic fibrosis

Congenital hepatic fibrosis (CHF) is a rare developmental disorder, mostly autosomal recessive in inheritance, primarily affecting the renal and hepatobiliary systems. The underlying abnormality is ductal plate malformation (DPM), producing irregularly shaped proliferating intrahepatic bile ducts and periportal fibrosis ultimately leading to PHT. A majority (64%) are associated with autosomal recessive polycystic kidney disease (ARPKD), caused by mutations in the PKHD1 gene encoding for fibrocystin/polycystin protein, which is essential for maintenance of 3-dimensional tubular architecture of renal and biliary epithelia, thus leading to fusiform dilatations of the renal collecting duct and DPM [150]. Another 25.6% of CHF are associated with Caroli disease or syndrome and <1% with Type V choledochal cyst; remaining 9.5% are isolated CHF [150].

Several other mutations and genetic syndromes have been described [151]. Median age at diagnosis ranges from 0 to 20 years, with ARPKD and Caroli phenotypes presenting early with renal insufficiency (74%) [150,152]. Presentation with PHT and cholangitis, although not mutually exclusive, is seen in 52–86% and 34% of cases, respectively. Esophageal varices and hypersplenism are present in 40–78% and 44–75%, respectively [150–153]. Ascites, hepatic encephalopathy and HPS are rare. There is increased predisposition to cholangiocarcinoma [150]. There is no correlation between renal function and PHT or severity of liver disease in ARPKD/CHF subtype [152,153]. Liver functions are essentially preserved except in the setting of cholangitis and variceal bleed [153]. Imaging (USG and MRCP) reveals dilatation of biliary system (70%) and enlargement of left lobe, splenomegaly with or without hepatic and renal cysts [151]. There is paucity of data on survival, but mortality is primarily related to sepsis, cholangiocarcinoma, variceal bleeding, and very rarely liver failure [150]. PHT is managed primarily with endotherapy and occasionally surgical shunt. Among various transplant options – single organ (liver or kidney) or combined liver/kidney (CLKT) – the decision is based on the age of onset, severity of PHT and renal insufficiency. But, considering high risk of cholangitis and renal insufficiency post isolated kidney and liver transplantation, respectively, CLKT is the best available option in symptomatic cases [150]. Neonatal presentation is the best predictor of need for CLKT in such setting [152].

Nodular regenerative hyperplasia

Nodular regenerative hyperplasia (NRH) constitutes around 27% and 14% of cases of NCPH in Europe and Japan, respectively [154]. Overall incidence in general population as per autopsy studies is 2.6% – the rate is 7 times more in people above 80 years of age [155]. Various chemotherapeutic and immunosuppressant drugs, hematological, autoimmune, inflammatory and neoplastic disorders are associated with NRH. Pathogenesis appears to be related to adaptive hyperplastic reaction of hepatocytes in response to mechanical or functional abnormalities of portal hepatic blood flow [154–157]. Pathologically, there is partial or complete transformation of the hepatic parenchyma into small regenerative nodules (size 1–3 mm), which sometimes coalesce to form large nodules. Evidence of regeneration with absence of fibrous septae between the nodules characteristically differentiates NRH from cirrhosis. Hypertrophied hepatocytes are located at the center, whereas atrophic ones at the periphery [154]. Hemodynamically, PHT in NRH is presinusoidal – HVP is below 12 mmHg in 75%, whereas PV pressure is high [157]. Clinically, a majority of NRH patients remain asymptomatic; symptomatic ones present with features of PHT and preserved liver functions [154]. Imaging features are non-specific – on USG, nodules appear hypoechoic or isoechoic with sonoluscent rim; on contrast enhanced CT, they are isodense or hypodense in both arterial and portal venous phases; while on contrast enhanced MR, they are hyperintense on T1- and isointense on T2-weighted images [154]. Treatment is directed towards primary disease. PHT is managed by endotherapy, surgical shunt or TIPSS [154,157]. Survival primarily depends on underlying disease and is not related to PHT or varices [156].

Review

Key Points

- Next to cirrhosis, NCPH is a common cause of PHT
- Two disease entities in NCPH, namely NCPF/IPH and EHPVO are distinct diseases, presenting with features of PHT – variceal bleed, splenomegaly and near normal liver functions. Likely pathogenesis is early age portal inflammation/infection in a prothrombotic individual
- Diagnosis needs exclusion of cirrhosis in NCPF/IPH and presence of portal cavernoma in EHPVO
- Slow hepatic dysfunction due to parenchymal extinction and portal biliopathy is a late event in EHPVO
- Effective management of PHT and its complications results in excellent 5 and 10 years survival

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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